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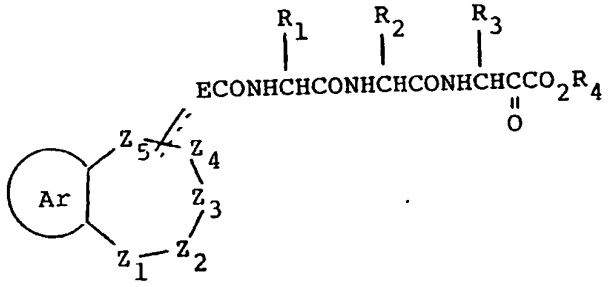
(54) Renin inhibitors and antiviral agents.

(57) Compounds of formula (I), and pharmaceutically acceptable salts thereof:



(I)

having renin inhibitor activity, a process for their preparation and their use as pharmaceuticals.

EP 0 445 467 A1

PHARMACEUTICALS

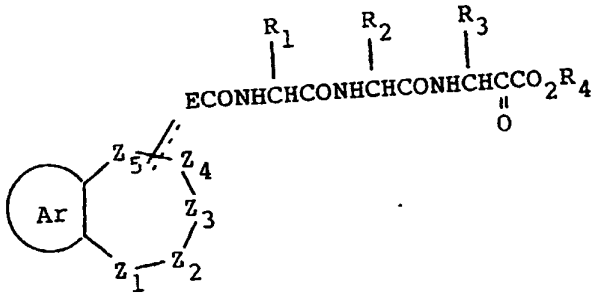
The invention relates to novel compounds having pharmacological activity, to processes for their preparation, to pharmaceutical preparations containing them and to their use in medicine.

Renin is a natural enzyme, disorders in relation to which are implicated in many cases of hypertension. It is released into the blood from the kidney, and cleaves from a blood glycoprotein a decapeptide known as angiotensin-I. Circulating angiotensin-I is cleaved in plasma, and in lung, kidney and other tissues to an octapeptide, angiotensin-II, which raises blood pressure both directly by causing arteriolar constriction and indirectly by stimulating release of the sodium-retaining hormone aldosterone from the adrenal gland and thus causing a rise in extracellular fluid volume. The latter effect is caused by angiotensin-II itself or a heptapeptide cleavage product angiotensin-III.

Inhibitors of renin have been described as useful in the treatment of hypertension.

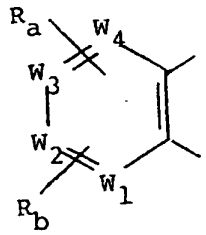
A group of compounds has now been discovered, which inhibit the enzyme renin and therefore have potential blood pressure lowering activity, useful in the treatment of hypertension. Compounds having an associated mechanism of action have also been described as possessing anti-retroviral activity and the present compounds may therefore be of potential use in the treatment of diseases caused by retroviruses including human immunodeficiency virus (HIV-1 and 2) and HTLV I and II. They may also be of potential use in the treatment of other cardiovascular disorders, such as congestive heart failure, and have beneficial effects on learning and memory and mood elevation activity, of potential use in the treatment of CNS disorders such as Alzheimer's disease and depression; they may also be of potential use in the treatment of glaucoma.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:

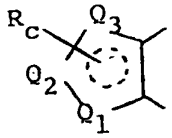


(I)

wherein
the Ar ring is of sub-formula (a) or (b):

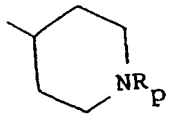


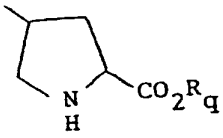
(a)

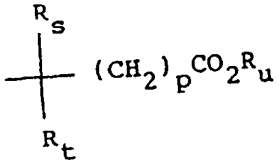


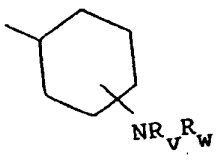
(b)

one or two of W_1, W_2, W_3 and W_4 is CH, N or NO (such that if two are NO then these are are W_1 and W_4), and the others are CH, CR_a or CR_b;
one of Q_1, Q_2 and Q_3 is S and the other two are CH and CR_c;
either Z_1 and Z_2 are absent and Z_3, Z_4 and Z_5 and the carbon atoms to which Z_3 and Z_5 are attached, form a 5-membered non-aromatic heterocyclic ring; or
Z_1 is absent and Z_2, Z_3, Z_4, Z_5 and the carbon atoms to which Z_2 and Z_5 are attached, form a 6-membered non-aromatic heterocyclic ring; or
Z_1, Z_2, Z_3, Z_4 and Z_5 and the carbon atoms to which Z_1 and Z_5 are attached, form a 7-membered non-aromatic heterocyclic ring;
E is absent or is $(CH_2)_n$ or $CH(CH_2)_{n-1}$ wherein n is 1 to 4;
R_a and R_b are independently selected from hydrogen or a substituent;
R_1 is CH_2R_9 wherein R_9 is optionally substituted aryl or heteroaryl;
R_2 is $CHR_{10}R_{11}$ wherein R_{10} is hydrogen or methyl and R_{11} is C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted aryl or heteroaryl, or R_{11} is amino, C_{2-7} alkanoylamino, 2-oxopyrrolidinyl, 2-oxopiperidinyl or C_{1-6} alkoxycarbonylamino;
R_3 is CH_2R_{12} wherein R_{12} is C_{1-6} alkyl or C_{3-8} cycloalkyl or phenyl;
R_4 is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4} alkyl or a group of structure c), d), e) or f):

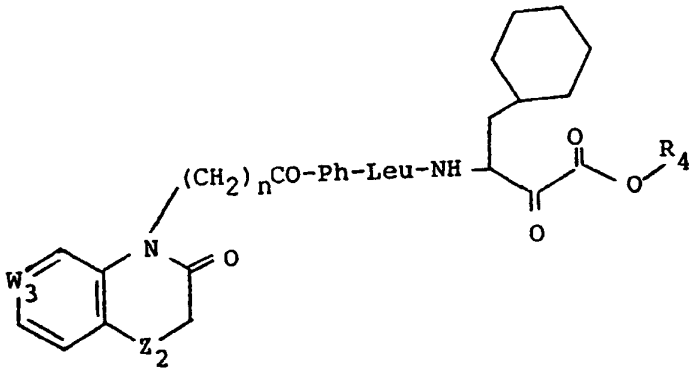
c) 

d) 

e) 

f) 

wherein
R_p, R_q, R_s, R_t, R_u, R_v and R_w are selected from hydrogen or C_{1-6} alkyl; or NR_vR_w is 1-imidazolyl; and



Compound/ Ex. No.	W_3	Z_2	n	R_4
Ex. 2	BOC-$NHCH_2$-C	O	2	i_{Pr}
Ex. 3	H_2NCH_2-C	O	2	i_{Pr}
Ex. 4	N	S	2	i_{Pr}
Ex. 5	N	S	3	i_{Pr}
Ex. 6	N	S	2	*

*4-(1-methylpiperidinyl)

Example 2

Isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate

This material was formed from isopropyl 2-(1-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 5(f)) (0.21g) following the procedure of Example 1. Chromatography on silica gel using methanol/chloroform (0-5% methanol, gradient) gave the title compound (0.14g) as a white solid.

NMR (δ) ($CDCl_3$): 0.7-1.05 (8H, m), 1.05-1.4 (11H, m), 1.45 (9H, m), 1.5-1.8 (8H, m), 1.85 (1H, m), 2.55 (2H, m), 2.9-3.2 (2H, m), 4.0-4.65 (8H, m), 5.15 (2H, m), 6.25-6.7 (1H, m), 6.85-7.0 (2H, m), 7.0-7.35 (8H, m).

Example 3

Isopropyl 3-(3-(6-(aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate.2TFA.1.5H_2O

This material was formed from isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-

benzoxazin-4-yl)-propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate(Example 2) (0.12g), following the procedure of Description 4(b). This gave the title compound (0.093g) as a white solid.

NMR (δ) ($DMSOd_6$): 0.7-1.0 (7H, m), 1.0-1.4 (12H, m), 1.4-1.9 (9H, m), 2.45 (m), 2.75 (1H, m), 2.85-3.1 (1H, m), 3.85-4.1 (3H, m), 4.1-4.4 (1H, m), 4.5-4.7 (3H, m), 4.7-4.85 (0.5H, m), 5.05 (0.5H, m), 6.0 (0.5H, m), 6.35 (0.5H, m), 7.0-7.1 (2H, m), 7.1-7.3 (5.5H, m), 7.35 (0.5H, m), 8.0-8.15 (2H, m), 8.15-8.5 (2H, m).

Analysis: $C_{40}H_{55}N_5O_8.C_2HF_3O_2.1.5H_2O$ requires C,57.7; H,6.8; N,8.00%. Found: C,57.6; H,6.7; N,7.7%.

M.S. (m/z) (FAB) (M+1) = 734 (consistent with m.w. of free base = 733).

Example 4

Isopropyl 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate.$2H_2O$

This material was formed from isopropyl 2-(1-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)-propanoyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 6(c)) (0.27g) following the procedure of Example 1. Chromatography on silica gel using methanol/chloroform (0-2% methanol, gradient) gave the title compound (0.12g) as a white solid.

NMR (δ) ($DMSOd_6$): 0.65-1.0 (8H, m), 1.0-1.3 (10H, m), 1.35 (2H, m), 1.4-1.95 (8H, m), 2.45 (2H, m), 2.75 (1H, m), 2.9 (1H, m), 3.1 (0.5N, m), 3.55 (2H, dd), 3.9-4.1 (2H, m), 4.25 (1H, m), 4.35 (1H, m), 4.55 (1H, m), 4.75 (1H, m), 5.0 (0.5H, m), 7.1-7.3 (5H, m), 7.45 (1H, m), 8.05 (0.5H, m), 8.15 (1H, dd), 8.2-8.35 (1.5H, m), 8.35-8.45 (0.5H, m), 8.5 (1H, m).

Analysis: $C_{38}H_{51}N_5O_9S.2H_2O$ requires C,60.2; H,7.3; N,9.2%. Found: C,60.1; H,7.0; N,9.1%.

M.S. (m/z) (FAB) (M+1) = 722 (consistent with m.w. = 721).

Example 5

Isopropyl 3-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)butanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate

This material was formed from isopropyl 2-(1-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)-butanoyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 7(c)) (0.22g), following the procedure of Example 4.

Analysis: $C_{39}H_{53}N_5O_7S.2H_2O$ requires C,60.7; H,7.4; N,9.1% Found: C,60.7; H,7.5; N,9.1%

M.S. (m/z)(FAB)(M+1) = 736 (consistent with m.w. of free base = 735).

Example 6

4-(1-Methylpiperidinyl) 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate

This material was formed from 4-(1-methylpiperidinyl)2-(1-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 8(e)) (0.37g), following the procedure of Example 4.

M.S. (m/z) (FAB) (M+1) = 777 (consistent with m.w. of free base = 776).

Biological Data

In vitro human renin inhibition

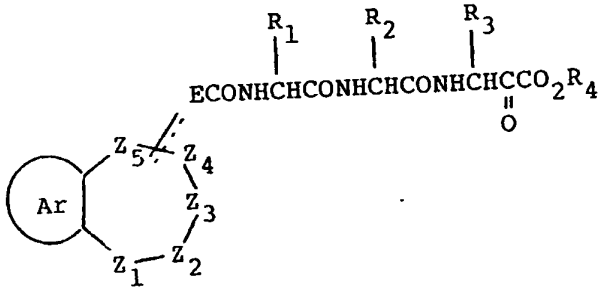
Renin inhibitory activity was estimated as the percentage change in renin activity in human plasma in the presence and absence of compound. The source of plasma was blood taken from healthy volunteers. Renin activity was defined by the difference in angiotensin I levels between two halves of a sample, one incubated at 37° and the other at 4° for 2 h. Angiotensin I levels were measured using a ^{125}I- angiotensin I radioimmuno- assay kit (NEN/DuPont, Stevenage). Results were calculated as the mean of at least two, duplicate determinations and IC_{50} values were calculated by linear regression analysis of at least three concentrations of compound.

The results were as follows:

Compound	IC_{50} (nm)
E1	15
E3	34
E4	5

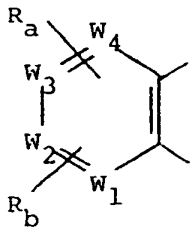
Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

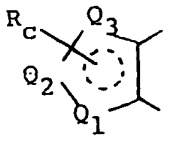


(I)

wherein
the Ar ring is of sub-formula (a) or (b):



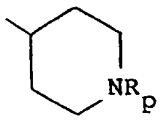
(a)

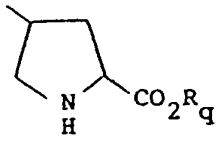


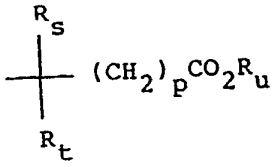
(b)

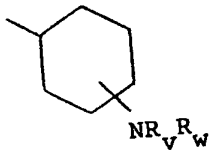
one or two of W_1, W_2, W_3 and W_4 is CH, N or NO (such that if two are NO then these are are W_1 and W_4), and the others are CH, CR_a or CR_b;
one of Q_1, Q_2 and Q_3 is S and the other two are CH and CR_c;
either Z_1 and Z_2 are absent and Z_3, Z_4 and Z_5 and the carbon atoms to which Z_3 and Z_5 are attached, form a 5-membered non-aromatic heterocyclic ring; or
Z_1 is absent and Z_2, Z_3, Z_4, Z_5 and the carbon atoms to which Z_2 and Z_5 are attached, form a 6-membered non-aromatic heterocyclic ring; or

Z_1, Z_2, Z_3, Z_4 and Z_5 and the carbon atoms to which Z_1 and Z_5 are attached, form a 7-membered non-aromatic heterocyclic ring;
E is absent or is $(CH_2)_n$ or $CH(CH_2)_{n-1}$ wherein n is 1 to 4;
R_a and R_b are independently selected from hydrogen or a substituent;
R_1 is CH_2R_9 wherein R_9 is optionally substituted aryl or heteroaryl;
R_2 is $CHR_{10}R_{11}$ wherein R_{10} is hydrogen or methyl and R_{11} is C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted aryl or heteroaryl, or R_{11} is amino, C_{2-7} alkanoylamino, 2-oxopyrrolidinyl, 2-oxopiperidinyl or C_{1-6} alkoxycarbonylamino;
R_3 is CH_2R_{12} wherein R_{12} is C_{1-6} alkyl or C_{3-8} cycloalkyl or phenyl;
R_4 is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4} alkyl or a group of structure c), d), e) or f):

c) 

d) 

e) 

f) 

wherein
R_p, R_q, R_s, R_t, R_u, R_v and R_w are selected from hydrogen or C_{1-6} alkyl; or NR_vR_w is 1-imidazolyl; and
the dashed line represents an optional bond (when E is present).

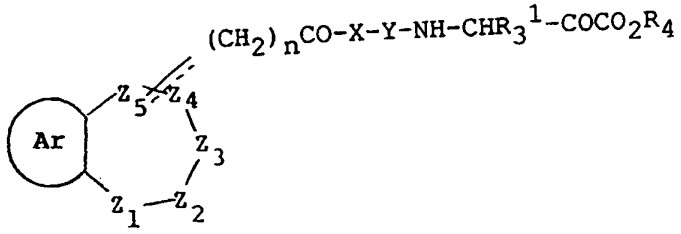
2. A compound according to claim 1 wherein Z_1 and Z_2 are absent, Z_3 is CO, Z_4 is N, Z_5 is CH and E is attached at Z_4.

3. A compound according to claim 1 wherein the Ar ring is of sub-formula (a), W_3 is N and W_1, W_2 and W_4 are CH, CR_a or CR_b, Z_2 is S, Z_3 is CH_2, Z_4 is CO, Z_5 is N and E is attached at Z_5.

4. A compound according to any one of claims 1 to 3 wherein one of R_a and R_b in sub-formula (b) is hydrogen and the other is CH_2NH_2, CO_2H or $CH_2NHCH_2CO_2H$, or R_c in sub-formula (b) is hydrogen.

5. A compound according to any one of claims 1 to 8 wherein the amino acid residue containing R_2 is Leu, β-pyrazolylalanine or His.

6. A compound according to claim 1 of formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

wherein X is Phe;
Y is Leu or His;
R_3' is cyclohexylmethyl; and
the remaining variables are as defined in claim 1.

7. A compound according to any one of claims 1 to 10 wherein E is $(CH_2)_n$ and E is attached at Z_4 or Z_5.

8. A compound according to any one of claims 1 to 11 wherein the carbon atom in R_4 adjacent CO_2, is either a secondary or tertiary carbon atom.

9. A compound according to claim 1, selected from the group consisting of

isopropyl 3-((2,3-dihydro-1,1-dioxobenzothiophene-3-yl)acetyl-Phe-Leu-amino)-4-cyclohexyl-2-oxobutanoate,

isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)-amino-4-cyclohexyl-2-oxobutanoate,

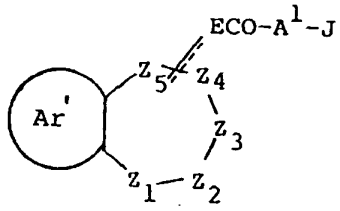
isopropyl 3-(3-(6-(aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate,

isopropyl 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxo-butanoate,

isopropyl 3-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)butanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxo-butanoate, and

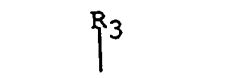
4-(1-methylpiperidinyl) 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)-amino-4-cyclohexyl-2-oxobutanoate.

10. A process for the preparation of a compound according to claim 1, which process comprises reacting a reagent of formula (III):



(III)

wherein Ar' is Ar as defined in claim 1, but substituted by R_a', R_b' in sub-formula (a) and by R_c' in sub-formula (b), wherein R_a', R_b' and R_c' are R_a, R_b and R_c respectively or groups or atoms convertible thereto. A^1 is absent or represents an appropriate amino acid or dipeptide unit; J is OH or a leaving group; and the remaining variables are as hereinbefore defined; with a reagent of the formula (IV):



(IV)

wherein
A^2 is absent or represents an appropriate amino acid or dipeptide unit, such that A^1 + A^2 is -NHCHR$_1$CONHCHR$_2$CO-; T is an optionally protected carbonyl group; and the remaining variables are as hereinbefore defined; and thereafter, if desired or necessary deprotecting (T or within A^1 or A^2) of the products, and/or converting Z_1, Z_2, Z_3, Z_4 or Z_5 to other Z_1, Z_2, Z_3, Z_4 or Z_5, R_a'/R_b'/R_c' in Ar' to R_a, R_b, and/or R_c and/or W_1, W_2, W_3 or W_4 in Ar' when N to NO; and/or forming a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, and a pharmaceutically acceptable carrier.

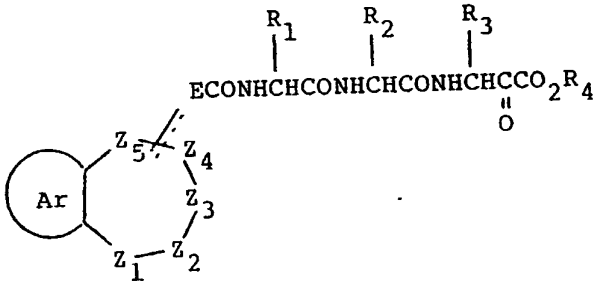
12. A compound according to any one of claims 1 to 9 for use as an active therapeutic substance.

13. A compound according to any one of claims 1 to 9 for use in the treatment of hypertension.

14. Use of a compound according to any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of hypertension.

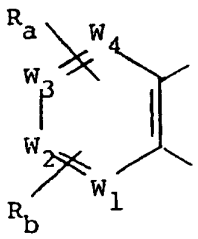
Claims for the following Contracting State: ES

1. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof:

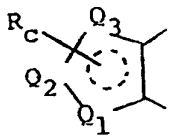


(I)

wherein
the Ar ring is of sub-formula (a) or (b):

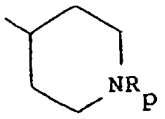


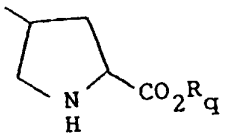
(a)

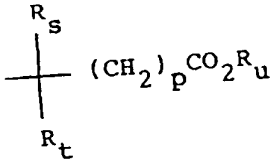


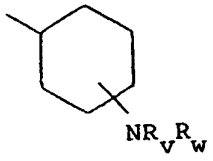
(b)

one or two of W_1, W_2, W_3 and W_4 is CH, N or NO (such that if two are NO then these are are W_1 and W_4), and the others are CH, CR_a or CR_b;
one of Q_1, Q_2 and Q_3 is S and the other two are CH and CR_c;
either Z_1 and Z_2 are absent and Z_3, Z_4 and Z_5 and the carbon atoms to which Z_3 and Z_5 are attached, form a 5-membered non-aromatic heterocyclic ring; or
Z_1 is absent and Z_2, Z_3, Z_4, Z_5 and the carbon atoms to which Z_2 and Z_5 are attached, form a 6-membered non-aromatic heterocyclic ring; or
Z_1, Z_2, Z_3, Z_4 and Z_5 and the carbon atoms to which Z_1 and Z_5 are attached, form a 7-membered non-aromatic heterocyclic ring;
E is absent or is $(CH_2)_n$ or $CH(CH_2)_{n-1}$ wherein n is 1 to 4;
R_a and R_b are independently selected from hydrogen or a substituent;
R_1 is CH_2R_9 wherein R_9 is optionally substituted aryl or heteroaryl;
R_2 is $CHR_{10}R_{11}$ wherein R_{10} is hydrogen or methyl and R_{11} is C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted aryl or heteroaryl, or R_{11} is amino, C_{2-7} alkanoylamino, 2-oxopyrrolidinyl, 2-oxopiperidinyl or C_{1-6} alkoxycarbonylamino;
R_3 is CH_2R_{12} wherein R_{12} is C_{1-6} alkyl or C_{3-8} cycloalkyl or phenyl;
R_4 is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4} alkyl or a group of structure c), d), e) or f):

c) 

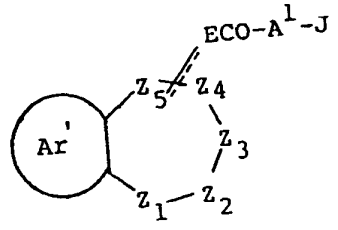
d) 

e) 

f) 

wherein
R_p, R_q, R_s, R_t, R_u, R_v and R_w are selected from hydrogen or C_{1-6} alkyl; or NR_vR_w is 1-imidazolyl; and

the dashed line represents an optional bond (when E is present);
which process comprises reacting a reagent of formula (III):



(III)

wherein Ar' is Ar as defined in claim 1, but substituted by R_a', R_b' in sub-formula (a) and by R_c' in sub-formula (b), wherein R_a', R_b' and R_c' are R_a, R_b and R_c respectively or groups or atoms convertible thereto. A^1 is absent or represents an appropriate amino acid or dipeptide unit; J is OH or a leaving group; and the remaining variables are as hereinbefore defined; with a reagent of the formula (IV):

(IV)

wherein
A^2 is absent or represents an appropriate amino acid or dipeptide unit, such that A^1 + A^2 is $-NHCHR_1CONHCHR_2CO-$; T is an optionally protected carbonyl group; and the remaining variables are as hereinbefore defined; and thereafter, if desired or necessary deprotecting (T or within A^1 or A^2) of the products, and/or converting Z_1, Z_2, Z_3, Z_4 or Z_5 to other Z_1, Z_2, Z_3, Z_4 or Z_5, R_a'/R_b'/R_c' in Ar' to R_a, R_b, and/or R_c and/or W_1, W_2, W_3 or W_4 in Ar' when N to NO; and/or forming a pharmaceutically acceptable salt thereof.

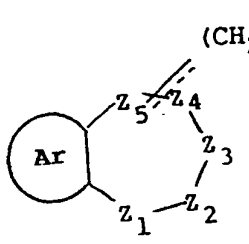
2. A process according to claim 1 wherein Z_1 and Z_2 are absent, Z_3 is CO, Z_4 is N, Z_5 is CH and E is attached at Z_4.

3. A process according to claim 1 wherein the Ar ring is of sub-formula (a), W_3 is N and W_1, W_2 and W_4 are CH, CR_a or CR_b, Z_2 is S, Z_3 is CH_2, Z_4 is CO, Z_5 is N and E is attached at Z_5.

4. A process according to any one of claims 1 to 3 wherein one of R_a and R_b in sub-formula (b) is hydrogen and the other is CH_2NH_2, CO_2H or $CH_2NHCH_2CO_2H$, or R_c in sub-formula (b) is hydrogen.

5. A process according to any one of claims 1 to 8 wherein the amino acid residue containing R_2 is Leu, β-pyrazolylalanine or His.

6. A process according to claim 1 for the preparation of a compound of formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

wherein
X is Phe;
Y is Leu or His;
R_3^1 is cyclohexylmethyl; and
the remaining variables are as defined in claim 1.

7. A process according to any one of claims 1 to 10 wherein E is $(CH_2)_n$ and E is attached at Z_4 or Z_5.

8. A process according to any one of claims 1 to 11 wherein the carbon atom in R_4 adjacent CO_2, is either a secondary or tertiary carbon atom.

9. A process according to claim 1, for the preparation of a compound selected from the group consisting of

isopropyl 3-((2,3-dihydro-1,1-dioxobenzothiophene-3-yl)acetyl-Phe-Leu-amino)-4-cyclohexyl-2-oxobutanoate,

isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)-amino-4-cyclohexyl-2-oxobutanoate,

isopropyl 3-(3-(6-(aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate,

isopropyl 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxo-butanoate,

isopropyl 3-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)butanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxo-butanoate, and

4-(1-methylpiperidinyl) 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)-amino-4-cyclohexyl-2-oxobutanoate.

10. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of hypertension.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 3104

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 296 581 (SQUIBB & SONS INC.) * Claims 1,10,11 *	1-10	C 07 K 5/02 C 07 K 5/06 A 61 K 37/64

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 K
A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	14 March 91	DEFFNER C-A.E.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document